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VPI/97-101CIP CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Joseph L. Kim, et al.
Application No.	:	09/303,216
Group Art Unit	:	1631
Examiner	:	Marianne P. Allen
Filed	:	April 30, 1999
For	:	CRYSTALS OF HEPATITIS C VIRUS HELICASE OR FRAGMENTS THEREOF COMPRISING A HELICASE BINDING POCKET

Cambridge, Massachusetts
November 25, 2002

Commissioner for Patents
Washington, D.C. 20231

PETITION UNDER 37 C.F.R. § 1.137(b) TO REVIVE AN UNINTENTIONALLY ABANDONED APPLICATION

Sir:

Pursuant to 37 C.F.R. § 1.137(b), applicants hereby petition for revival of the above United States Application 09/303,216, filed April 30, 1999 ("the application"). In the application, applicants filed a May 28, 2002 Response to a February 26, 2002, Final Office Action. The application unintentionally became abandoned as of **August 26, 2002** because of applicants' failure to either: 1) file a Notice of Appeal by August 26, 2002; or 2) to file a continuation application by August 26, 2002.

Accordingly, as required by 37 C.F.R. § 1.137(b), this petition is accompanied by a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114.

The Director is hereby authorized to charge to Deposit Account No. 50-0725 payment of the following fees required in connection with this petition:

(1) a $710.00 filing fee for the RCE (37 C.F.R. § 1.17(e); and

(2) a $1280.00 petition fee required under 37 C.F.R. § 1.17(m).

The Director is also authorized to charge any deficiencies in the above fees or any other fees required in connection with this petition to Deposit Account No. 50-0725. A duplicate copy of this Petition is transmitted herewith.

The delay in filing a RCE from August 26, 2002 until the filing of this grantable petition under 37 C.F.R. § 1.137(b) was unintentional.

Accordingly, applicants respectfully request that this petition be granted and the application be revived. Early and favorable consideration of this petition is respectfully requested.

Respectfully submitted,

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BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE

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Nandakumar Govindaswamy is hereby given limited recognition under 37 CFR §10.9(b) as an employee of Vertex Pharmaceuticals, Inc. to prepare and prosecute patent applications wherein the patent application is assigned to Vertex Pharmaceuticals, Inc., and the attorney or agent of record in the applications is a registered practitioner who is an employee of Vertex Pharmaceuticals, Inc. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Nandakumar Govindaswamy ceases to lawfully reside in the United States, (ii) Nandakumar Govindaswamy's employment with Vertex Pharmaceuticals, Inc. ceases or is terminated, or (iii) Nandakumar Govindaswamy ceases to remain or reside in the United States on an H-1B visa.

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Expires: June 30, 2003

Harry Moatz,
Director of Enrollment and Discipline

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Cambridge, MA 02178
May 28, 2002

RESPONSE TO FINAL OFFICE ACTION

This is in response to the final Office Action dated February 26, 2002, in the above-identified application. This response is timely because May 26 was a Sunday and May 27 was a Federal holiday (Memorial Day). 37 C.F.R. §1.7(a).

Please amend the application as follows:

IN THE CLAIMS

Cancel claims 7 to 24 without prejudice.

REMARKS

The Examiner states that the application "contains claims 7-24 drawn to an invention nonelected with traverse" and that "[a] complete reply to the final rejection must include cancelation of non-elected claims...." Applicants have complied with this requirement by canceling claims 7-24 without prejudice.

Claims 1-3 are pending in this application and have been rejected under 35 U.S.C. §112, first paragraph for "not reasonabl[y] provid[ing] enablement for all crystallizable [compositions] and crystallized complexes encompassed by the claims." Specifically, the Examiner states that the scope of the single-stranded oligonucleotide in these compositions and complexes ("a single-stranded oligonucleotide consisting of between 6 and 12 nucleotides") is not enabled.

The Examiner has rejected applicants' argument that the single-stranded oligonucleotide has limited contact with the protein (see applicants' December 3, 2001 Amendment). She points to the specification at pages 66-68 which, according ot the Examiner, refers to the fact that in the HCV NS3 helicase-$d(U)_8$ crystal "at least $dU_{4-5, 7-8}$ interacts with the helicase by hydrogen bonding." Therefore, the Examiner concludes that the "identity of the single stranded oligonucleotide would seem to make a difference." Applicants traverse.

As pointed out in applicants' December 3, 2001 Amendment, the specification clearly states that:

> "Sequence specific interactions with the DNA bases are not observed within the central binding cavity of the helicase." (emphasis added; p. 71, lines 1-2).

The hydrogen bonding interaction observed by applicants is entirely consistent with this statement. Hydrogen bonding is not specific to deoxyuridine. As those of skill in the art well know, the ability of nucleotides to accept a hydrogen bond from a protein or water surrounding the nucleotide is due to the presence of oxygen atoms in the phosphate group on the nucleotide backbone – a common feature of all nucletoides [see, e.g., D. E.

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Metzler, "Biocehmistry", Academic Press, New York, NY, p. 98, right column, item (3), (1977); copy enclosed]. It is that backbone phosphate hydrogen bond acceptor present in all nucleotides, not some structural feature unique to dU_8, that is responsible for the interactions between the oligonucleotide and the HCV NS3 helicase. This is set forth in the application:

> "Interaction between the ssDNA and enzyme are mostly confined to the DNA backbone, as would be expected for a nonspecific protein-nucleic acid complex.... Interestingly, these contacts arise from symmetrically equivlanet resdiues in these two domains [domains 1 and 2 of the helicase], so that protein contacts to the dU4 and dU5 backbone phosphates are nearly identical to those to the dU7 and duU8 phosphates.
>
> At the 3' end of the DNA the dU8 phosphate is stabilized by a hydrogen bond with Thr-269 Oγ.... Equivalent contacts to the dU5 phosphate are made by the Arg-393 main chain NH and Thr-411 Oγ.... The dU7 phosphate accepts a hydrogen bond from the Val-232 NH and interacts with the Ala-233 NH and Ser-231 Oγ via a bridging water molecule. The direct and water mediated main chain interactions are duplicated by Lys-371 and Lys-372 from domain 2 to the dU4 phosphate. Ser-370, the equivalent residue in domain 2 to Ser-231, makes a water mediated contact to the dU3 phosphate rather than dU4. Superposition of domains 1 and 2 of HCV helicase reveals that the residues involved in phosphate contacts are structurally equivalent (Figure 6)...." (emphasis added; p. 67, line 9 – page 68, line 12).

The interactions between the backbone phosphate residues in dU_8 and HCV helicase observed by applicants can and would be expected to occur independent of the actual nucleotide make-up of the oligonucleotide. All nucleotides have a backbone phosphate and as such all nucleotides could accept hydrogen bonds from the HCV NS3 helicase in the same manner as those in dU_8. This is further supported by the experimental evidence that poly(A), poly(G) and poly(C) all bind to the HCV NS3 helicase [Y. Gwack et al., Biochem. Biophys. Res. Comm., 225, pp. 654-69 (1996) (see particularly, p. 656, Fig 2D and p. 659, first paragraph) (copy previously submitted)].

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The structural features of the HCV NS3 helicase-dU_8 interactions, and in particular the hydrogen bonding between the nucleotide backbone phosphate and certain amino acids in the helicase, as set forth in the application provide requisite assurance that any single stranded oligonucleotide of between 6 and 12 baseswould be capable of forming a crystallized complex with an HCV NS3 helicase protein. This is so irrespective of the individual nucleotides that make up such an oligonucleotide. Accordingly, claims 1-3 are fully enabled by the specification as filed and meet the requirements of 35 U.S.C. §112, first paragraph.

Applicants respsectfully request that the Examiner consider the foregoing remarks and allow pending claims 1-3 to pass to issue.

Respectfully submitted,

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BIOCHEMISTRY

The Chemical Reactions of Living Cells

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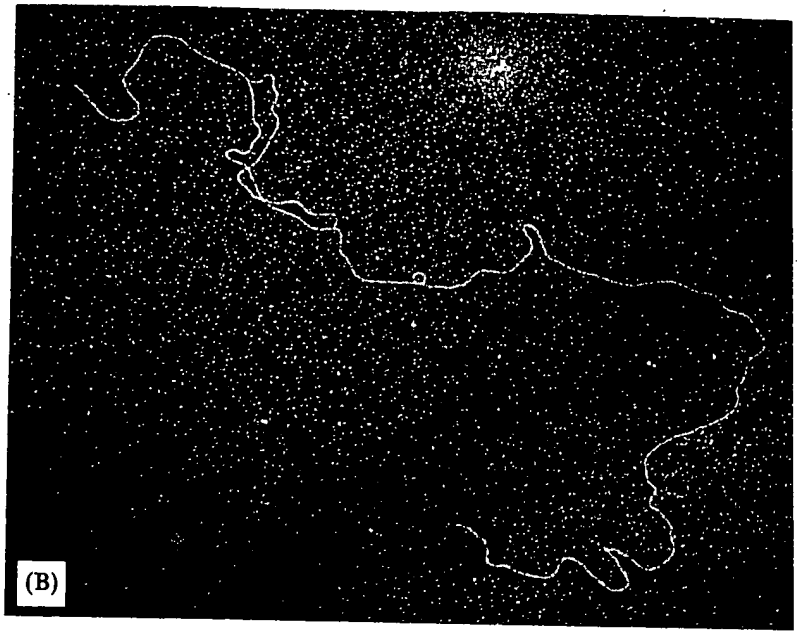

Fig. 2-23 (B) Electron micrograph of a DNA molecule (from a bacterial virus (bacteriophage T7) undergoing replication. The viral DNA is a long (~14 μm) duplex rod containing about 40,000 base pairs. In this view of a replicating molecule an internal "eye" in which DNA has been duplicated is present. The DNA synthesis was initiated at a special site (origin) about 17% of the total length from one end of the duplex. The DNA was stained with uranyl acetate and viewed by dark field electron microscopy. Micrograph courtesy J. Wolfson and D. Dressler.

in the opposite plane by a *twofold axis of rotation* **(dyad axis).** This symmetry element, which arises from the antiparallel arrangement of the chains, makes the DNA molecule from the outside look identical whether viewed from one end or the other—and whether viewed as a model by the human eye or through contact with an enzyme which might act on the molecule. Actually, the two chains are not identical, and the genetic information can be read off from the surfaces exposed in the major groove (see Fig. 2-23).

Note the dimensions of the double helix (Fig. 2-23). The diameter, measured between phosphorus atoms, is just 2.0 nm. The pitch is 3.4 nm. There are 10 base pairs per turn. Thus, the rise per base pair is 0.34 nm, just the van der Waals radius of an aromatic ring (Table 2-1). It is clear that the bases are "stacked" in the center of the helix. A typical gene of 1000 bases would be a segment of DNA rod about 340 nm long (Fig. 2-23B).

As is appropriate for the cell's master blueprint, DNA in the double helix is extremely stable. Despite its long length, it does not often break in nature. Several factors contribute to this stability. (1) The pairs and triplets of hydrogen bonds between the bases. (2) The van der Waals attraction between the flat bases which stack together. (3) The fact that on the outside of the molecule are many oxygen atoms, some negatively charged, which are able to form strong hydrogen bonds with water or with special proteins surrounding the molecule. (4) The ability to form various superhelices (see below).

The fact that DNA can also exist as a paracrystalline A form (in which the bases are tilted and there are 11 base pairs per turn) suggests the possibility that both conformations may be important in nature. While **RNA** molecules usually exist as single chains, they often form **hairpin loops** consisting of double helices in the A conformation.[71] The B conformation is impossible because of the presence of the 2'-hydroxyl groups on the ribose rings in RNA. Transient "hybrid" DNA-RNA double helices are also thought to exist within cells and they too may be constrained to the A structure. It is noteworthy that the A structures differ from the B structure of DNA in having a large (~0.8 nm) hole along the axis and a very deep major groove.[71a] The base pairs do not lie on the axis as in Fig. 2-23.

The best known forms of RNA are the low

Docket No.: VPI/97-101 CIP CON US

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I hereby certify that the following documents:

1. Petition Under 37 CFR 1.137(b) to Revive an Unintentionally Abandoned Application (2 pages);
2. Request for Continued Examination (RCE), (in duplicate) with a copy of The response filed on 5/28/02; and
3. this return postcard receipt.

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington D.C. 20231

Karen DiRocco
(type or printed name of person mailing document(s))

Karen DiRocco
(signature of person mailing document(s))